REMARKS

Status of the Claims

Claim 18 has been amended by incorporating the limitations of claim 28. Claims 31-35 have been added, and are supported by the originally filed claims. As a result, claims 18-27 and 30-35 are pending and under examination.

Claim Rejections

Claim 18-28 and 30 have been rejected under 35 USC § 103 over *Willoughby et al.* (WO 94/23725) in view of *Pressato et al.* (WO 97/07833). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Applicants submit that the Examiner, for the following reasons, has failed to establish a proper *prima facie* case of obviousness.

1. The Legal Standard for an Obviousness Analysis

The touchstone for a proper obviousness analysis under 35 USC § 103 is "predictability". The guidelines set forth in MPEP § 2143 set forth seven rationales for considering obviousness. In addition to the so-called "TSM" rationale, all six of the other rationales require the Examiner to establish "predictability", such as "combining prior art elements according to known methods to yield predictable results" (rationale A, emphasis added).

This type of analysis is in accord with the fundamental rationale established by the Supreme Court which stated that "when the question is whether a patent claiming a combination of elements of prior art is obvious" the relevant question is "whether the improvement is more than predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007).

Applicants submit that in the present case the Examiner has not established the requisite "predictability" and, in fact, the evidence would establish just the opposite.

2. The Cited Prior Art References Fail to Teach, Suggest, or Render Obvious, the Present Invention

The present invention is directed to a method for the treatment of primary and secondary tumors by inhibiting angiogenesis by applying at the tumor site a biomaterial comprised of a benzyl ester of hyaluronic acid. The Examiner will note that claim 18 has been amended to recite the nature of the biomaterial as previously set forth in claim 28. As such, the biomaterial of the invention is particularly a non-woven felt, sponge, microsphere, film or membrane.

Willoughby et al. disclose compositions with anti-angiogenic activity comprising hyaluronic acid (HA) or a derivative thereof, and also disclose compositions comprising HA or a derivative thereof in a mixture with a non-steroidal anti-inflammatory drug, such as diclofenac. *Willoughby et al.*, however, do not teach any benzyl esters of hyaluronic acid as in the present invention.

In an attempt to cure this deficiency, the Examiner has combined *Willoughby et al.* with *Pressato et al.* which describe benzyl esters of hyaluronic acid. Applicants submit, however, that the Examiner's attempted combination of *Willoughby et al.* with *Pressato et al.* is not proper.

First of all, HA contains several esterifiable groups and it can form, for example, alcohol or acid esters, aromatic or aliphatic esters, short or long-chain aliphatic esters, and other types of possible "esters". Nevertheless, *Willoughby et al.* merely generically mentions "esters" of hyaluronic acid without any guidance as to the selection of any particular types or individual "esters". This is not a situation wherein there are a "finite" identifiable number of "predictable" solutions that could provide a reasonable expectation of success as in rationale (E) of the USPTO obviousness guidelines. In the present case, there are a vast number of possible "esters" of hyaluronic acid and the Examiner has not provided any reasoning as to why one skilled in the art

reading *Willoughby et al.* would be lead to particularly utilize benzyl esters of hyaluronic acid as in the present invention.

A proper reading of *Willoughby et al.* would actually teach against the prior art combination suggested by the Examiner. *Willoughby et al.* report evidence of anti-angiogenic activity only for HA sodium salt **in combination** with an anti-inflammatory drug. The results in *Willoughby et al.* show that HA alone does not induce any significant effect on tissue vascularity; whereas the combination of HA-Diclofenac significantly reduces vascularity (see page 17, lines 30-34). With these results, one skilled in the art seeking to provide an alternative method for the treatment of tumors would have focused on the combinations of HA and the anti-inflammatory agent and would not have sought to modify the HA component, which the test results show was not active.

This reasoning is further supported by test data in *Alam et al.* (Enclosure 1). This publication discusses the same test data as reported in the *Willoughby et al.* reference and *Alam et al.* conclude that HA alone does not have any effect on the examined parameters of vascular density and vascular index (see page 409, column 1, lines 1-7 below Table 1; col. 2, 2nd par. and page 410, 1st col., lines 13-16). To explain the efficacy of simultaneous administration of HA and Diclofenac, *Alam et al.* hypothesized that HA behaves as a drug delivery system without any pharmacological effect *per se* (see page 40, the right hand column, lines 14-15). Again, this teaching that HA alone does not have the desired pharmacological effect on anti-angiogenic activity would not have lead one skilled in the art to modify the HA component, and to specifically select benzyl esters, as in the present invention.

Experimental results subsequent to the filing of the present application have further buttressed this position. *Willhauck et al.* (Enclosure 2) report on studies utilizing non-woven tissues of HA benzyl esters. Those experiments demonstrated that non-woven tissues of HA benzyl esters possess an anti-invasive activity towards tumors, because they induce the formation of granulation tissue and of a fibrotic connective tissue wherein myofibrils accumulate (see the abstract), thereby forming connective tissue capable of modulating components of the connective stroma in a way that chemotaxis of tumor cells angiogenesis are blocked (see the discussion,

lines 1-9 and 17-22). In other words, this article demonstrates that the formation of a granulation tissue is necessary for preventing chemotaxis and angiogenesis. On the contrary, *Willoughby et al.* teach reducing angiogenesis by reducing a granulation tissue. Specifically, *Willoughby's.* test model comprises forming a granulation tissue, then treating with HA or an association thereof with an anti-inflammatory drug, and then evaluating not only the reduction of the vascular volume, but also the granuloma's weight (see pages 16-18 and 30, as well as the "analysis" section on pages 20 and 23)[1]. Thus, one skilled in the art would recognize that the properties of *Willoughby's* desired associations are actually completely opposite to those of the scaffolds/biomaterials of the present invention.

Finally, *Willoughby et al.* teach that the described products are applied to the patient's skin and/or exposed tissue or are administered systemically. The present invention, on the other hand, relates to the use of a biomaterial in the form of a non-woven felt, sponge, microsphere, film or membrane which is applied to the tumor site, and can particularly be administered after surgical removal of a tumor. *Willoughby et al.* simply do not teach or suggest use of the biomaterials of the present invention.

In summary, while *Willoughby et al.* teach the anti-angiogenic activity of combinations of HA and a non-steroidal anti-inflammatory drug, the Examiner's attempted combination of *Willoughby et al.* with *Pressato et al.* does not render the present invention obvious because:

(a) *Willoughby et al.* teach that HA alone is not active for anti-angiogenic activity, so one skilled in the art would not be lead to select HA benzyl esters for this purpose.

(b) *Willoughby et al.* teach reducing angiogenesis by reducing a granulation tissue, whereas, the non-woven tissues of HA benzyl esters have the opposite activity of inducing the formation of a granulation tissue, so again one skilled in the art would not be led to use HA benzyl ester for the purpose of the present invention.

[1] Enclosure 3 is a copy of a relevant page from a scientific and technical dictionary to show that "granuloma" means a tissue with significant "granulation".

(c) *Willoughby et al.* teach only the administration of compositions either topically or systemically, and do not suggest the application of biomaterials to the tumor site, as in the present invention.

In view of the above, reconsideration and withdrawal of the rejections are requested.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of $1,050.00 is attached hereto.

If the Examiner has any questions concerning this application, the Examiner is requested to contact Leonard R. Svensson, Reg. No. 30,330 at the telephone number of (858) 792-8855. Facsimile communications may be sent to the undersigned at the facsimile number of (858) 792-3785.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Dated: October 1, 2008

Respectfully submitted,

By _____
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